



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: February 2, 2019

Subject: **Tetraniliprole.** Report of the Residues of Concern Knowledgebase Subcommittee (ROCKS).

PC Code: 090097

Decision No.: 527795

Petition No.: 7F8558

Risk Assessment Type: NA

TXR No.: NA

MRID No.: NA

DP Barcode: D447757

EPA File Symbol.: 264-RROG, 264-RROE, 264-RROU, 279-GAEG, 279-GAEI, and 279-GAEU

Regulatory Action: Section 3 Registration

Case No.: NA

CAS No.: 1229654-66-3

40 CFR: NA

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The ROCKS conducted an electronic review to discuss the residues of concern for the insecticide tetraniliprole in plant commodities, livestock commodities, and drinking water. This is the first registration and tolerance request for tetraniliprole. The summaries of toxicological, residue chemistry, and environmental fate data prepared by the tetraniliprole risk assessment team were considered.

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I. Background

Tetraniliprole is a new insecticide developed by Bayer CropSciences (Bayer) and FMC Corporation. Tetraniliprole belongs to the anthranilic diamide class of pesticides, which control insects through unregulated activation of ryanodine receptor (RyR) channels leading to internal calcium store depletion that impairs regulation of muscle contraction. Insects exposed to anthranilic diamide exhibit general lethargy and muscle paralysis followed ultimately by death (Cordova et al., 2006). Its target pests are insects from the families of Lepidoptera, Coleoptera, and Diptera. It also controls some sucking pests.

It was developed for control of certain insect pests by seed treatment in corn (field, pop, sweet and seed production). It is also proposed for control of certain insect pests by foliar and soil application to tuberous and corm vegetables (crop group 1C), leafy vegetables (crop group 4-16), brassica head and stem vegetables (crop group 5-16), fruiting vegetables (crop group 8-10), citrus fruit: orange subgroup 10-10A, lemon/lime subgroup 10-10B, grapefruit subgroup 10-10C, pome fruit (crop group 11-10), stone fruit (crop group 12-12), small fruit vine climbing subgroup, except fuzzy kiwi (crop subgroup 13-07F), tree nuts (crop group 14-12), field corn, popcorn, sweet corn, soybeans, and tobacco. The review is a joint review with Pesticide Management Regulatory Agency (PMRA)/Canada.

Plant metabolism studies were conducted in diverse crops: apples, potatoes, lettuce, and rice after foliar broadcast treatments, on tomato after soil drench treatment, on potato after seed piece treatment, on corn after seed treatment, including a tobacco pyrolysis study. The residues were qualitatively similar for all crops. Tetraniliprole was a major component of the residue in all crops. Livestock metabolism studies were conducted with lactating goat and laying hen. Crop field trial studies and analytical methods are adequate.

In addition, studies of soil and aquatic metabolism under aerobic and anaerobic conditions, along with aqueous and soil photolysis, hydrolysis, and aquatic field dissipation studies were conducted to understand the environmental fate of tetraniliprole.

II. Committee Recommendation

Table 1. Summary of Metabolites and Degradates to be Included in the Risk Assessment and Tolerance Expression.			
Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Not applicable ¹	Tetraniliprole
	Rotational Crop	Not applicable ¹	Tetraniliprole
Livestock	Ruminant	Not applicable ¹	Tetraniliprole
	Poultry	Not applicable ¹	Tetraniliprole
Drinking Water		Not applicable ¹	Not applicable

¹ No hazard has been identified in the toxicological studies conducted on tetraniliprole and the metabolites/degradates are not likely to be more toxic than the parent compound, therefore, residue definitions for a quantitative risk assessment do not need to be established.

III. Summary of Materials Considered

Please see Appendix 1 for the chemical structures and nomenclature of tetraniliprole and its metabolites.

A. Hazard Information

Tetraniliprole produced adverse effects in dose levels which were approaching or slightly above the limit dose (1000 mg/kg/day). The only exceptions were the subchronic and chronic dog toxicity studies, where marginal decrease in body weights and non-adverse incidence of salivation in dogs were observed at 500 mg/kg/day (highest dose tested). In addition, no systemic or dermal toxicity was seen in a 28-day dermal toxicity study at the limit dose. Therefore, no toxicological endpoints were identified for parent tetraniliprole (ToxSAC review on 05/17/2018).

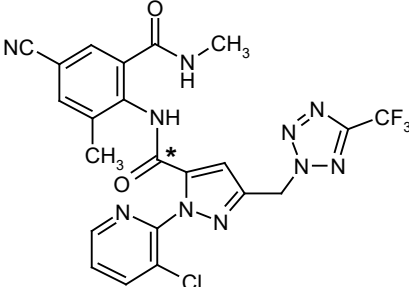
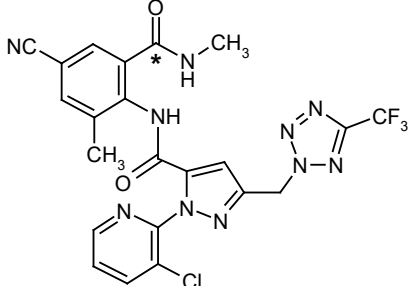
The rat metabolism data show that tetraniliprole was rapidly absorbed and distributed. For all low-dose tests, and the test with males at 20 mg/kg-bw, the maximum plasma concentration (C_{max}) was reached approximately 1 hr after administration of tetraniliprole, and for females at 20 mg/kg-bw, approximately 7 hr after administration. A limited absorption was seen for rats at high-dose levels (20 and 200 mg/kg-bw) compared to rats at the low-dose level (2 mg/kg-bw).

Most of the metabolites (90-108% of the administered dose) were identified. Unchanged parent was the major component in all test groups, and accounted for approximately 51-66% of the dose for the 2 mg/kg-bw groups and approximately 89-108% of the dose for the 200 or 20 mg/kg-bw groups. Metabolites were detected at 1-9% of the dose (2 mg/kg-bw).

Unchanged parent was the major component in the urine (0.53-2.20%). At the low dose and high dose, unchanged parent accounted for about 94-99% of the identified metabolites present in feces in males and females. In contrast, unchanged parent in the test groups administered 2 mg/kg-bw only accounted for approximately 50-70% of the identified metabolites. The increase in excretion of unchanged parent, concomitant with the increases in dose, further demonstrates decreased absorption at the higher doses.

B. Plant Metabolism

The metabolism of tetraniliprole was investigated in commodities from different crop categories: apples (fruits), potatoes (root crops), lettuce (leafy vegetables) and rice (cereal) after foliar broadcast treatments; and different type of treatments: soil drench (tomato); seed treatment (potato and corn); and granular (rice). Two different radiolabels were used in separate experiments in all plant studies (except potato seed piece and field corn seed treatment-one radiolabel was used) and confined rotational crop studies. These label positions are shown below:

Chemical structure	 <p>* Denotes the position of the ¹⁴C-label.</p>
Radiolabel position	[pyrazole-carboxamide- ¹⁴ C]
Chemical structure	 <p>* Denotes the position of the ¹⁴C-label.</p>
Radiolabel position	[phenyl-carbamoyl- ¹⁴ C]

i. Primary Crops

The residues were qualitatively similar for all crops. The major residues (>10% TRR) found in primary (treated) plants are parent tetraniliprole (BCS-CL73507) and BCS-CL73507-N-methyl-quinazolinone (BCS-CQ63359) in all plant matrices investigated. BCS-CL73507-N-methyl-quinazolinone was a major component in tomato (leaves, fruits), potato tuber, paddy rice (forage, straw), and field corn stover. However, BCS-CL73507-N-methyl-quinazolinone was insignificant compared to the parent and quantifiable only in rice straw.

ii. Rotational Crops

The metabolism of tetraniliprole in representative rotational crops (wheat, turnips and Swiss chard) from three consecutive rotations was investigated. [pyrazole-carboxamide-¹⁴C]- or (2) [phenyl-carbamoyl-¹⁴C]- tetraniliprole were each formulated as an SC formulation and soil applied to confined plots of sandy loam soil at a rate of 210 g ai/ha (0.190 lb ai/A) (1x maximum seasonal rate). The crops were each sown at 30, 168, and 286 days after soil application.

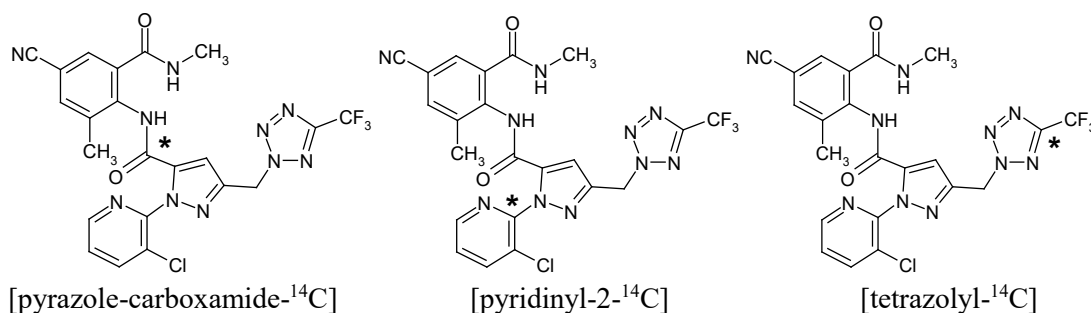
The majority of the total radioactive residues (TRRs) of all raw agricultural commodity (RACs) were extractable by conventional extraction methods using a mixture of acetonitrile/water and formic acid. The residues in the extracts ranged from 77-99% of the TRRs. The TRRs were > 0.01 ppm in all matrices from each label at all plantback intervals (PBIs), except turnip leaves and roots (30-day PBI). In the first rotation (PBI= 30d), tetraniliprole was a predominant residue in all RACs ranging from 40-88% of the TRRs (0.001-0.152 ppm); in the second rotation (PBI=168d), tetraniliprole was a predominant residue in wheat matrices and Swiss chard ranging from 26-60% of the TRRs (0.004-0.040 ppm); and in the third rotation (PBI= 286d), tetraniliprole was a predominant residue in wheat (forage, hay, straw), and Swiss chard (immature) ranging from 16-56% of the TRRs (0.003-0.017 ppm). Metabolite BCS-CL73507-N-methyl-quinazolinone was quantifiable only in some feedstuffs, but at lower levels than the

parent. The confined rotational crop studies for tetraniliprole adequately define the nature of the residue in three crop types planted in treated soil at intervals of 30, 168, and 286 days. The metabolites found in the crop rotation study correspond to metabolites found in the plant metabolism studies.

The limited and field rotational crop studies indicate non-quantifiable levels of parent residues in/on several crops at a PBI of 30 days. The studies also indicate quantifiable levels of parent residues in livestock feed stuffs such as alfalfa, foliage of legume vegetables, and foliage of cereal grains. Metabolite BCS-CL73507-N-methyl-quinazolinone was quantifiable only in some feedstuffs, but at lower levels than the parent. Inadvertent or indirect tolerances for these rotational crops are needed at a PBI of 30 days (Table 2). These data demonstrate that parent is taken up by plants grown in soil treated with tetraniliprole.

C. Livestock Metabolism

Three studies on the metabolism of tetraniliprole in lactating goats and laying hens were conducted with the test compound radiolabelled with ^{14}C either in the [pyrazole-carboxamide]-, the [pyridinyl-2]- or the [tetrazolyl]-moiety as shown below (* denotes the label position):



i. Ruminants

The goat was orally dosed once daily for five consecutive days at an average of 21 to 38 mg/kg dry feed in the diet. The animals were sacrificed about 6 hours after the last administration. Milk was collected in the morning immediately prior to each administration, about eight hours later in the afternoon, and finally approximately 1 hour before sacrifice.

Following the administration of the test compounds, approximately 68-74% of the administered dose was recovered, of which 64-71% was in the excreta, and the remainder postulated to be in the gastrointestinal tract. Approximately 1.8-2.4% of the administered dose was each in the organs/tissues, and 1.1-1.3% in the total milk (0 to 102 hrs).

The overall TRRs were highest in liver (0.88-1.2 ppm), with decreasing amounts in fat (0.39-0.60 ppm), total milk (0.22-0.37 ppm), kidney (0.24-0.33 ppm), and muscle (0.09-0.12 ppm). Parent compound was a predominant residue in milk (55-70% of the TRRs; 0.16-0.27 ppm), muscle (65-68% of the TRRs; 0.06-0.08 ppm), fat (24-30% of the TRRs; 0.09-0.16 ppm), liver (53-62% of the TRRs; 0.54-0.64 ppm), and kidney (59-71% of the TRRs; 0.17-0.20 ppm). Residues in milk ranged from 0.14-0.51 ppm from day-1 until sacrifice for all radiolabels.

The majority of the radioactivity was found in skim milk (94-98% of the TRRs; 0.397-0.496 ppm) in comparison to cream (2-6% of the TRRs; 0.010-0.024 ppm).

The predominant residues were tetraniliprole and BCS-CL73507-N-methyl-quinazolinone in muscle, fat, kidney, and milk. Only tetraniliprole was identified as major in goat liver. BCS-CL73507-benzylalcohol (BCS-CZ91631) was a main component in milk only. BCS-CL73507-benzylalcohol is assumed to have comparable toxicity to the parent.

ii. Poultry

The hens were orally dosed once daily for 14 consecutive days at an average of 18 to 19 mg/kg dry feed in the diet. This dose level represents an exaggerated rate relative to the estimated maximum possible dietary burden to hens. Samples of excreta were collected daily. Samples of eggs were collected twice daily. The hens were sacrificed approximately 6 hours after the final dose.

The total % administered dose was 92-93%, of which 91-92% was excreted. The remaining amount of radioactivity (approx. 7%) was postulated to be present in the gastrointestinal tract at sacrifice, due to the short period of time between the last administration and sacrifice (approx. six hours). An average total amount of 0.2% of the total dose was measured in the eggs, and 0.2-0.3% in organs/tissues at sacrifice.

The overall TRRs were highest in liver (0.485-0.766 ppm), with decreasing amounts in kidney (0.098-0.332 ppm), eggs (0.063-0.069 ppm), fat (0.028-0.095 ppm), skin (0.035-0.078 ppm), and muscle (0.017-0.031 ppm). Eggs from ovaries/oviduct amounted to 0.218-0.245 ppm.

The parent was a predominant residue in eggs (10-14% of the TRRs; 0.008-0.012 ppm), muscle (10% of the TRRs; 0.002 ppm), and fat (26-55% of the TRRs; 0.012-0.025 ppm).

In laying hens, the predominant residues were tetraniliprole (eggs, muscle, and fat), and BCS-CL73507-despyridyl-N-methyl-quinazolinone (eggs, fat, and liver). A waiver for poultry feeding study was submitted. Based on a low estimated dietary burden in poultry and low transfer of residues from the metabolism studies, there is a low potential for exposure from these analytes in the human diet. However, if additional uses with poultry feed items are requested, a poultry feeding study would be required. The predominant residues should be monitored accordingly in a poultry feeding study.

D. Drinking Water

Please refer to the memorandum from the Environmental Fate and Effects Division (EFED) for detail information regarding the environmental transformation products of tetraniliprole (of the Residues of Concern Knowledgebase Subcommittee (ROCKS) DP Barcode 446504).

Tetraniliprole is considered slightly soluble to moderately soluble and moderately mobile based on FAO solubility and mobility classification scheme. It is not expected to volatilize from dry surfaces, water or moist soil. Tetraniliprole's main route of degradation is hydrolysis at neutral (40-60 days SFO DT₅₀, pH 7) and basic pHs (0.76-1.3 days SFO DT₅₀, pH 9) and aqueous photolysis (10.6-day light adjusted-SFO DT₅₀, pH 4). It is stable to hydrolysis at a pH of 4.

Photolysis of tetraniliprole in soil resulted in a day light adjusted SFO DT₅₀ of 70 days. Aerobic and anaerobic aquatic metabolism studies show partition of tetraniliprole to the sediment and degradation in the total water:sediment system with DT₅₀ of 11.2 days (SFO) to 925 days (DFOP as conservative value). The compound is slightly persistent to persistent (Goring *et al.* 1975), based on aerobic and anaerobic soil metabolism studies (DT₅₀ from 25.1 days (IORE) to 380 days (DFOP)) and terrestrial field dissipation studies (DT₅₀ from 30 to 1,000 days).

One of two processes are proposed to initiate the transformation of tetraniliprole, cyclization or hydrolysis. Cyclization of tetraniliprole results in the formation of its N-methyl-quinazolinone degradate (BCS-CQ63359), which is the main degradate formed by hydrolysis of tetraniliprole and the main transformation product in soil and aqueous system. Generally, it increased up to study termination in all laboratory studies except for photolysis. Other major transformation products observed in aerobic and anaerobic studies in soil include: BCS-CR74541 (up to 48.1% AR), BCS-CU81055 (up to 12.3% AR) and BCS-CT30673 (up to 11.3% AR). In addition, BCS-CY28906 (19.8% AR at 10 days) and BCS-CY28900 (73.1% AR at 11 days) are formed by photolysis in natural water (pH 8) and aqueous buffer (pH 4). In general, the major metabolites are structurally similar to the parent compound.

IV. Rationale

Residues of Concern for Tolerance Enforcement: Parent tetraniliprole and BCS-CL73507-N-methyl-quinazolinone (BCS-CQ63359) were the predominant residues observed in primary crops, rotational crops, and livestock. However, BCS-CL73507-N-methyl-quinazolinone was insignificant compared to the parent and quantifiable only in feedstuffs. Based on this, HED recommends parent tetraniliprole as the residues of concern for tolerance enforcement. It is important to note that tolerances are being established for trade purposes only.

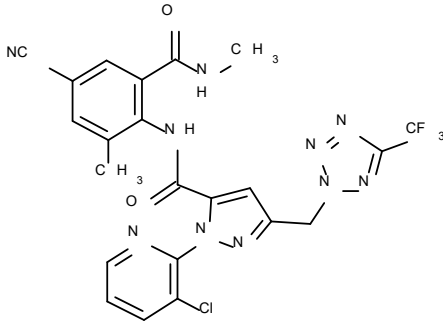
Residues of Concern for Risk Assessment: Residues of concern in plants, livestock, and water were not selected for risk assessment purposes based on the absence of adverse effects at the highest doses tested in all of the required toxicity studies for tetraniliprole, and the structural similarity of major degradates/metabolites with the parent compound. Those that retain all the rings of the parent compound are expected to have the same or lesser toxicity and similar hazard. Based on this, no quantitative assessment is necessary for parent or degradates/metabolites at this time.

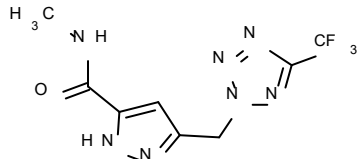
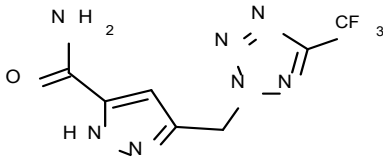
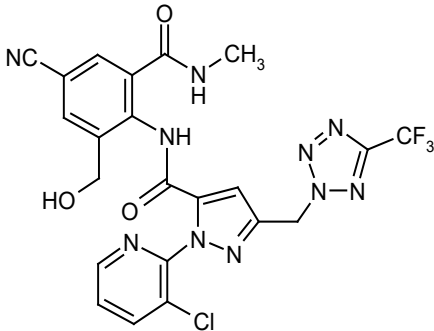
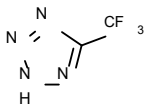
V. Recommended Tolerance Expression

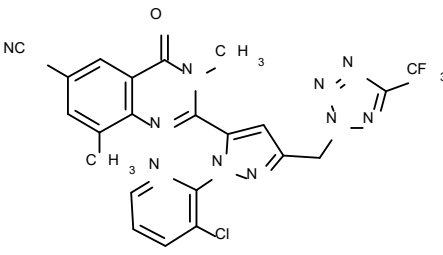
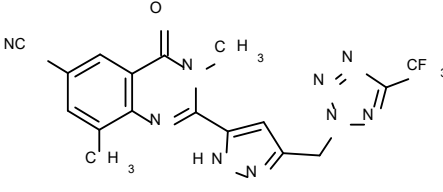
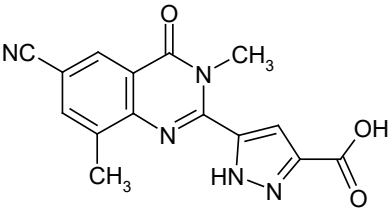
The ROCKS recommend the following language for the tolerance expression for primary crops, rotational crops, and livestock commodities:

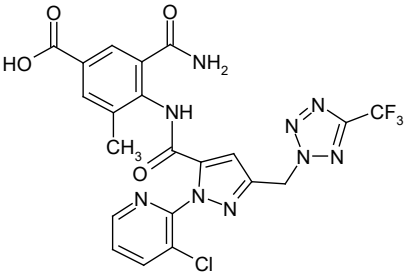
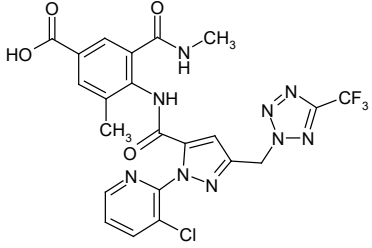
(a) *General (1).* Tolerances are established for residues of tetraniliprole, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only tetraniliprole 1-(3-chloro-2-pyridinyl)-N-[4-cyano-2-methyl-6-[(methylamino)carbonyl]phenyl]-3-[[5-(trifluoromethyl)-2H-tetrazol-2-yl]methyl]-1H-pyrazole-5-carboxamide in/on the following commodities.

Appendix 1. Tetraniliprole Major Metabolites Identified in the Metabolism Studies (plant (primary and secondary; and livestock)

Report Name	Chemical Structure	Major metabolites (>10% of TRRs)	
		%TRRs	ppm
BCS-CL73507 [Tetraniliprole]		<u>Hen:</u> Eggs: 10-14 Muscle: 10 Fat: 26-55	0.008-0.012 0.002 0.012-0.025
		<u>Goat:</u> Milk: 55-70 Liver: 53-62 Muscle: 65-68 Fat: 24-30 Kidney: 59-71	0.156-0.266 0.541-0.641 0.057-0.083 0.094-0.165 0.167-0.197
		<u>Tomato:</u> Leaves: 25-27 Fruit: 22-34	0.001-0.002 <0.001
		Lettuce: 99-100 Potato: 29-42	4.043-4.084 <0.001
		<u>Apple:</u> Leaves: 99 Fruit: 92-99	97.98 0.182-0.231
		<u>Rice:</u> Grain (F): 91-92 Grain (G): 22-48 Forage (F): 97-98 Forage (G): 79-81 Husks (F): 93-96 Husks (G): 78-83 Straw (F): 94-95 Straw (G): 77	0.022-0.037 0.001 1.268-2.537 0.007-0.009 1.954-2.417 0.015-0.020 4.309-4.112 0.054-0.075
		<u>Field corn:</u> Stover: 26	0.002
		<u>1st Rotation:</u> <u>Wheat:</u> Forage: 85-88 Hay: 59-68 Straw: 60-66	0.048-0.053 0.109-0.123 0.077-0.152
		<u>Turnip:</u> Leaves: 40-69 Roots: 48-54	0.003-0.004 0.001-0.002
		<u>Swiss chard:</u> Intermediate: 71-79 At maturity: 63-74	0.039-0.044 0.032-0.035

Report Name	Chemical Structure	Major metabolites (>10% of TRRs)	
		%TRRs	ppm
		<u>2nd Rotation:</u> <u>Wheat:</u> Forage: 46-60 Hay: 37-38 Straw: 38-57 <u>Swiss chard:</u> Intermediate: 34-39 At maturity: 26-30	0.014-0.015 0.023-0.024 0.038-0.040 0.006-0.007 0.004-0.006
		<u>3rd Rotation:</u> <u>Wheat:</u> Forage: 44 Hay: 24-52 Straw: 16-41 <u>Swiss chard:</u> Intermediate: 24-56	0.006 0.015 0.014-0.017 0.003-0.007
BCS-CL73507- pyrazole-5- <i>N</i> -methyl- amide		<u>Hen:</u> Muscle: 18-40	0.005-0.007
BCS-CL73507- pyrazole-5-amide		<u>Hen:</u> Muscle: 13	0.002
BCS-CL73507- benzylalcohol BCS-CZ91631		<u>Goat:</u> Milk: 11	0.042-0.045
BCS-CL73507- tetrazole and conjugate 1 – 3 of BCS-CL73057- tetrazole		<u>Hen:</u> Muscle: 29	0.009

Report Name	Chemical Structure	Major metabolites (>10% of TRRs)	
		%TRRs	ppm
BCS-CL73507- <i>N</i> -methyl-quinazolinone [BCS-CQ63359]		<u>Goat:</u> Milk: 11-13 Muscle: 23-28 Fat: 62-72 Kidney: 59-71	0.026-0.056 0.024-0.029 0.279-0.399 0.033-0.044
		<u>Tomato:</u> Leaves: 34-37 Fruits: 11-20	0.002 <0.001
		<u>Potato:</u> 13 <u>Rice:</u> Forage (G): 12 Straw (G): 11-14	<0.001 0.001 0.007-0.014
		<u>Field corn:</u> Stover: 17	0.001
		<u>1st Rotation:</u> Wheat hay: 13-14 Turnip roots: 13-16	0.023-0.028 0.001
		<u>2nd Rotation:</u> <u>Wheat:</u> Hay: 13 Straw: 13-22 <u>Swiss chard:</u> immature: 10	0.008 0.014-0.015 0.002
		<u>3rd Rotation:</u> Hay: 10 Straw: 22 <u>Swiss chard:</u> immature: 14	0.003 0.008 0.002
BCS-CL73507-despyridyl- <i>N</i> -methyl-quinazolinone [BCS-CY28894]		<u>Hen:</u> Eggs: 27-63 Fat: 63 Liver: 12	0.023-0.030 0.029-0.059 0.060
BCS-CL73507-despyridyl- <i>N</i> -methyl-quinazolinone-pyrazole-3-carboxylic acid		<u>1st Rotation:</u> <u>Swiss chard:</u> Immature: 11-15 At maturity: 12-16	0.006-0.008 0.005-0.008
		<u>2nd Rotation:</u> <u>Swiss chard:</u> At maturity: 11-12	0.002

BCS-CL73507-desmethyl-amide-carboxylic acid (BCS-CU81055)		<div> <u>1st Rotation:</u> <u>Turnip:</u> Leaves: 21 0.001 Roots: 18 0.001 </div> <div> <u>2nd Rotation:</u> <u>Wheat:</u> Forage: 21 0.006 Hay: 12 0.007 </div> <div> <u>Swiss chard:</u> Immature: 19 0.004 At maturity: 25 0.006 </div> <div> <u>3rd Rotation:</u> <u>Wheat:</u> Forage: 25 0.003 Hay: 20 0.013 Straw: 19 0.021 </div> <div> <u>Swiss chard:</u> Immature: 26 0.004 At maturity: 31 0.005 </div>
BCS-CL73507-carboxylic acid (BCS-CR74541)		<div> <u>1st Rotation:</u> <u>Turnip:</u> Leaves: 23 0.001 Roots: 13-19 <0.001 </div> <div> <u>2nd Rotation:</u> <u>Wheat:</u> Straw: 14 0.001 </div> <div> <u>Swiss chard:</u> Immature: 12-27 0.002-0.004 At maturity: 14-28 0.003-0.004 </div> <div> <u>3rd Rotation:</u> <u>Wheat:</u> Hay: 17 0.005 Straw: 11 0.004 </div> <div> <u>Swiss chard:</u> Immature: 11-14 0.002 At maturity: 12 0.002 </div>